

# Auxiliary or orthotopic liver transplantation for acute fatty liver of pregnancy: case series and review of the literature

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## Case series

The objective of this study was to present all cases of liver transplantation (LT) for acute fatty liver of pregnancy (AFLP) from 1979 through 2012 in the Netherlands and to review the literature.

### Orthotopic liver transplantation

The first case was a 30-year-old woman with a history of two uneventful pregnancies and deliveries. In the first trimester of her third pregnancy she had suffered temporarily from hyperemesis gravidarum. In 2002, in the 25th week of pregnancy, she presented elsewhere with jaundice, itching, upper abdominal pain, nausea, vomiting and fatigue. She then rapidly developed encephalopathy and disturbed clotting, and had a spontaneous vaginal delivery of a boy at 25 weeks with postpartum haemorrhage. The baby died the first day. Because bilirubin, International Normalised Ratio (INR) and encephalopathy further deteriorated, 4 days after delivery she was admitted to the intensive care unit of the Leiden University Medical Centre (LUMC). There was jaundice and severe hepatic encephalopathy with restlessness, and coma developed within 1 day (Opolon–Conn stage 4, EMV score 3). No signs of chronic liver disease and no Kaiser–Fleisher rings were present. An underlying autoimmune disorder, viral or metabolic causes such as Wilson disease were excluded. Abdominal Doppler ultrasound revealed hepatic steatosis but was otherwise normal. A liver biopsy showed some hepatocyte necrosis and evident steatosis, 80% microvesicular and 20% macrovascular, compatible with a diagnosis of AFLP. Laboratory and clinical findings are shown in Table 1.

The patient fulfilled King's College Hospital (KCH) criteria for LT.<sup>1</sup> She was placed on the high urgency waiting list for LT and was supported by continuous venovenous haemofiltration (CVVH) with molecular absorbent recirculating system (MARS), intravenous acetylcysteine and systemic cooling (35 °C) until orthotopic liver transplantation (OLT).<sup>2</sup> The next day she underwent OLT. Postoperatively, she developed renal insufficiency but CVVH was not necessary because renal function rapidly improved. She was discharged home on day 22 after OLT without further complications and with tacrolimus and mycophenolate mofetil as immunosuppressants. No long-chain hydroxacyl CoA dehydrogenase (LCHAD) mutations were detected.<sup>3</sup> She has remained well more than 10 years after OLT, without further pregnancies.

### Auxiliary liver transplantation

The other woman was 35 years of age, with a history of two spontaneous miscarriages. During her third pregnancy she presented in 2002 at another hospital at 37 weeks gestation with fatigue, drowsiness and nausea, haemodynamic instability and intra-uterine fetal death. Delivery was induced. Six days postpartum she was referred to LUMC with progressive liver failure with disturbed clotting, renal insufficiency, hypoglycaemia and haemodynamic instability. Within a day she developed hepatic coma (Opolon–Conn stage 4, EMV score 3) and brain oedema as evidenced by transcranial Doppler examination. Laboratory and clinical findings are indicated in Table 1. She did not fully comply with KCH criteria, but serum lactate was 8.9 mmol/L. Immediate treatment was started with CVVH with MARS, intravenous acetylcysteine and systemic cooling (35 °C).

**Table 1.** Laboratory findings prior to transplantation with reference ranges and King's College Hospital criteria in all published patients and the current two patients with liver transplantation for acute liver failure from AFLP. Data just before orthotopic (OLT) and auxiliary (AUX) liver transplantation respectively as derived from the publications

Reference	Case 1 Leiden	Case 2 Leiden	Ockner et al. <sup>16</sup>	Amon et al. <sup>17</sup>	Franco et al. <sup>18</sup>	Gill et al. <sup>19</sup> ****	Remiszewski et al. <sup>20</sup>	Luzar et al. <sup>21</sup> *****	Kong et al. <sup>22</sup>	Aso et al. <sup>23</sup>	Westbrook et al. <sup>24</sup> , Knight et al. <sup>10</sup> *****
Age of mother (years)	30	35	37	35	32	18	19	28	27	37	21–38
Gravida/para	3/2	3/2	2/1	3/1	2/1	1/0	N/A	N/A	2/1	1/0	N/A
Vaginal delivery (V)/ Section (S)	V	V	S	S	V twins	V	V	S	S	S	N/A
Birth at × weeks, alive/dead	25 D	37 D	37 A	x A	36 AA	33 D	33 D	28 A	34 A	38 A	33–38
Transplant × days after birth	5	8	4	3	4	3	10	5	4	3	N/A
(Estimated*) liver weight (g)	N/A	N/A	850	850	N/A	N/A	N/A	2100	N/A	N/A	N/A
Mother alive (A)/dead (D)	A	A	A	A	A	A	A	D	A	A	A
OLT/AUX/ILDT	OLT	AUX	OLT	OLT	AUX**	OLT	OLT	OLT	OLT	LDLT	OLT
INR (1.0)	4.9	1.8	1.7	5.9	>10	4.8	1.8	N/A	2.2	3.3	1.24–2.7
Albumin, g/l (30–40)	15	31	21	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Platelets × 10 <sup>9</sup> /l (150 –300)	54	97	82	52	63	173	12	N/A	N/A	N/A	21–54
Total bilirubin, µmol/l (0–18)	273	190	126	138	235	37	112	N/A	524	116	65–93
ALAT, U/l (0–45)	47	134	81	81	280	4112	82	N/A	23	126	3000–3739
ASAT, U/l (0–35)	119	50	88	88	141	6737	36	N/A	52	117	N/A
LDH, U/l (0–248)	379	2890	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
ALP, U/l (0–115)	97	117	299	N/A	N/A	341	N/A	N/A	702	N/A	N/A
GGT, U/l (0–55)	53	54	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Creatinine, µmol/l (64–104)	60	287	246	334	246	255	202	N/A	115	N/A	142–220
BUN, mmol/l (2.5–7.5)	6.3	16.4	N/A	N/A	N/A	N/A	N/A	N/A	16.6	N/A	N/A
Lactate mmol/l (0.5– 2.2)	2.4	8.9	N/A	N/A	N/A	8	N/A	N/A	N/A	N/A	2.6–18
pH (7.35–7.45)	7.49	7.39	N/A	7.37	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Bicarbonate, mmol/l (22–29)	28	18	N/A	13.6	N/A	21	N/A	N/A	N/A	N/A	N/A
Ammonia, mmol/l (11–48)	135	128	N/A	Normal	N/A	160	N/A	N/A	N/A	95	N/A
Encephalopathy grade (0/4)	4	4	3	2	3	4	4	N/A	4	4	1–4
Phosphate, mmol/l (0.90–1.50)	1.01	2.41	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A

Table 1. (Continued)

Reference	Case 1 Leiden	Case 2 Leiden	Ockner et al. <sup>16</sup>	Amon et al. <sup>17</sup>	Franco et al. <sup>18</sup>	Gill et al. <sup>19,***</sup>	Remiszewski et al. <sup>20</sup>	Luzar et al. <sup>21,****</sup>	Kong et al. <sup>22</sup>	Aso et al. <sup>23</sup>	Westbrook et al. <sup>24</sup> , Knight et al. <sup>10</sup> *****
KCH criteria fulfilled	Yes	No	No	Yes	No***	No	No	N/A	No	No	No
Jaundice >7 days before HE	Yes	Yes	Yes	Yes	No***	No	Yes	Yes	Yes	Yes	N/A
Age <10 or >40 years	No	No	No	No	No	No	No	No	No	No	No
INR >3.5 (PT.50 s)	Yes	No	No	Yes	Yes	Yes	No	N/A	No	No	No
Bilirubin >300 µmol/l	No	No	No	No	No	No	No	N/A	No	No	No
NonAnonB	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes

N/A, not available; LDLT, living donor liver transplantation; OLT, orthotopic liver transplantation; AUX, auxiliary liver transplantation; ALP, alkaline phosphatase; GGT, gamma glutamyltransferase; ALAT, alanine aminotransferase; ASAT, aspartate aminotransferase; KCH, King's College Hospital.

\*Measured weight or estimated by volume on CT scan.

\*\*Graft removed on day 7 after transplantation for hepatic artery thrombosis.

\*\*\*According to the description, the interval between jaundice and encephalopathy was probably <7 days.

\*\*\*\*AFLP combined with acetaminophen toxicity.

\*\*\*\*\*AFLP combined with Herpes Simplex Virus infection type 2.

\*\*\*\*\*In both reports the same AFLP patient with LT was included in the data range, thus combined data from four patients (one with AFLP) were presented.

She was placed on the high urgency waiting list for LT. The next day, auxiliary liver transplantation (AUX) was carried out, with a left partial graft (segments 2, 3 and half of 4) in the left upper abdomen and a renoportal anastomosis, leaving the native liver untouched, as described elsewhere.<sup>4</sup> An intra-operative native liver biopsy revealed severe steatosis, mixed micro- and macrovascular (50/50%), and was compatible with a diagnosis of AFLP. Postoperatively, CVVH was required and critical illness neuropathy developed. This resolved and the patient recovered within 3 weeks. Both livers were regularly assessed with hepatobiliary scintigraphy and computed tomography with volumetry and liver biopsies. Scintigraphy showed sufficient function of the graft and improving function of the native liver over time, and liver biopsies showed a significant reduction of steatosis in the native liver. This led to removal of the auxiliary liver on day 31 after AUX. This liver was re-used as an orthotopic graft in another recipient, as described elsewhere.<sup>5</sup> Tacrolimus and prednisolone were stopped. She went home on day 7 after graft explantation. No LCHAD mutations were found. Now, more than 10 years later, she leads a normal life with normal liver function, without further pregnancies.

## Discussion

Searching the databases from the three Dutch liver transplant centres revealed that in 33 years of liver transplantation in 1979–2012 in the Netherlands, there were two cases – one OLT and one AUX – from 2445 liver transplantations (<0.1%) for AFLP. Both had an excellent outcome. After AUX, the graft could be removed and immunosuppression stopped after regeneration of the native liver. The graft was then successfully used for OLT in another recipient.

After obtaining permission to search in the databases of the European Liver Transplant Registry and in the Euro-transplant database, under-reporting and wrong coding were found, preventing further European analysis.

AFLP can occur in the third trimester of pregnancy, with an estimated prevalence of 1:7000–13 000 deliveries. Maternal mortality of AFLP was 80% before 1980, and 18% in 1999, with a fetal mortality rate of 20–60%.<sup>6,7</sup> This improvement is probably due to many factors, such as improved intensive care and better obstetric care, including earlier termination of pregnancy.<sup>2,6–8</sup> Patients often present with epigastric pain, nausea and vomiting. Jaundice, hepatic encephalopathy, thrombocytopenia and disturbed clotting can be present, and subcapsular haematomas and liver rupture can occur. The Swansea criteria for diagnosing AFLP were validated in a prospective study.<sup>9,10</sup> Overlap with HELLP (haemolysis, elevated liver enzymes and low platelet count) syndrome can

exist. Treatment consists in accelerated delivery with correction of clotting and of hypoglycaemia, and most women recover. Infants receive an adjusted diet, rich in carbohydrates and low-fat, and long-term fasting is avoided.<sup>6,7</sup> In acute liver failure (ALF), early CVVH with cooling and intravenous antibiotics may reduce the incidence of brain oedema, one of the major causes of death in ALF.<sup>2</sup> MARS is still used in ALF but has no proven survival benefit. In contrast, plasmapheresis may be beneficial in AFLP, and this may also be true for ALF in general.<sup>11,12</sup>

Between August 2004 and August 2006 in the Netherlands there were 12 cases of severe maternal morbidity from AFLP, representing 0.47% of the 2552 cases of severe maternal morbidity from a total of 371 021 deliveries.<sup>13</sup> This gives an incidence of AFLP of 3.2 cases per 10 000 deliveries (95% CI 1.8–5.7). In this period no women died due to AFLP. If we extrapolate the 12 cases in these 2 years to 23 years, then this represents  $23 \times 12/2 = 138$  cases of severe maternal morbidity from AFLP. In the 23-year period 1983–2006, the maternal mortality rate from AFLP was 0.13 per 100 000 live births (95% CI 0.05–0.29), as reported in a retrospective study, while maternal death from AFLP occurred in six women (one in 1995, five in 2000–2001) from 538 cases (1%) of maternal death.<sup>14</sup> In four of these six cases, liver failure was mentioned as a cause of death. In the other two cases the deaths were likely related to the AFLP, but with diffuse intravascular coagulation (DIC) and with cardiac arrest as the cause. Two LTs for AFLP were performed in the Netherlands in 33 years; in 23 years this would be  $2 \times 23/33 = 1.4$ . Assuming that the two women we transplanted would otherwise have died, and adding the four cases of maternal death due to liver failure from AFLP to the above calculated incidence of LT of 1.4 in 23 years – assuming these patients could have been saved by LT – LT would have been required in  $4 + 1.4 = 5.4$  of 138 (3.9%) patients with severe morbidity from AFLP. Obviously, this is only a rough estimation: data do not span the same years, and it was assumed that all women who died from liver failure due to AFLP would benefit from LT, which may not be the case. Some may have been too sick to undergo LT. Furthermore, sepsis with jaundice and DIC can mimic ALF, and such patients should not be transplanted. A recent prospective study from the UK found severe morbidity from AFLP of 31 per 10<sup>6</sup> births.<sup>15</sup> This is in very good agreement with the severe AFLP incidence found in the Netherlands of 32 per 10<sup>6</sup> births.<sup>13</sup> In the UK, 0.7 deaths per 10<sup>6</sup> births were due to AFLP, with a survival-to-death ratio for AFLP of 70:1.<sup>15</sup> Thus in all the British cases with AFLP, including those less severe, a maximum of 1/71 (1.4%) women may need LT. This indeed is close to the case fatality rate for AFLP in the

UKOSS study of 1.8% (95% CI 0–9.4%).<sup>10</sup> In the Netherlands we included only cases of severe AFLP in the calculation above, which explains the difference between 3.9% and 1.4%, but the figures are within the same range.

In the UKOSS study, infant perinatal mortality in mothers with AFLP was around 10%.<sup>10</sup>

In total, 11 women, including the two Dutch cases, with LT for AFLP have been published, as summarised in Table 1.<sup>10,16–24</sup> Ten of the 11 survived. This may partially be publication bias, as it is possible that non-survivors were not published. Nevertheless, these data show that LT can be lifesaving in very severe AFLP without recovery after termination of pregnancy. Most transplants were performed within a week after delivery.

The decision to perform LT is a difficult one, especially as the KCH criteria for LT in ALF apparently do not fully apply to AFLP. This is due to aggressive correction of coagulopathy for bleeding complications, resulting in a lower INR, where age is below 40, and bilirubin often below 300 µmol/l, and the interval between development of jaundice and encephalopathy is usually shorter than a week.<sup>24</sup> Our data from the transplanted patients confirm this. Data from KCH also showed that in women with severe maternal morbidity requiring intensive care admission (almost all with AFLP or hypertensive disease in pregnancy), the presence of encephalopathy and lactic acidosis seem better than the KCH criteria to distinguish women requiring LT from those who will survive without LT.<sup>24</sup> Indeed, all women transplanted for AFLP shown in Table 1 had hepatic encephalopathy and in the few with measured serum lactate and ammonia, these values were elevated. This needs to be validated further. Especially as most patients with AFLP recover after delivery, better guidelines for indicating LT in AFLP are required.

Although OLT is the standard, an advantage of AUX for ALF is that in the majority of surviving patients the native liver regenerates, and withdrawal of immunosuppression is possible within a year, with removal of the graft or graft atrophy after deliberate chronic rejection.<sup>25,26</sup> In haemodynamically unstable women with 'toxic liver syndrome' due to cytokine release from liver necrosis, OLT may be preferred. As severe necrosis is unusual in AFLP, AFLP without improvement after delivery and with hepatic encephalopathy and elevated serum lactate and ammonia may be an ideal indication for AUX in haemodynamically stable women, but this needs further confirmation. AUX is a more complex operation than OLT with some more primary malfunction and vascular complications, but it may allow timely intervention and withdrawal of immunosuppression.

### Disclosure of interests

Full disclosure of interests available to view online as supporting information.

## Contribution to authorship

All individuals that qualified for authorship have been included and all those included qualify for authorship. JR, KWMB, MSA and BvH contributed to conception and design, interpreted the data, NF and JJB acquired the data, BvH and JR drafted the article, all authors revised the article critically for intellectual content and approved the final version to be published, and agreed to be accountable for all aspects of the work, ensuring that questions related to the accuracy or integrity of any part of the work were appropriately investigated and resolved.

## Details of ethics approval

Retrospective studies with anonymised reporting are by law exempt from approval by the institutional review board. Both patients gave informed consent for this report, which conformed to the ethical guidelines of the 1975 Declaration of Helsinki.

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